N-Confused Tetraphenylporphyrin and Tetraphenylsapphyrin Formation in One-Flask Syntheses of Tetraphenylporphyrin

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The yields of tetraphenylporphyrin (TPP), N-confused tetraphenylporphyrin (NC-TPP), and tetraphenylsapphyrin (TPS) were examined under diverse conditions in the one-flask room-temperature reaction of pyrrole and benzaldehyde. The conditions examined included TFA and BF_3-etherate catalysis, acid concentrations, pyrrole and benzaldehyde concentrations, pyrrole:benzaldehyde ratios, the addition of salt, and reaction times. The quantities of TPP, NC-TPP, and TPS were determined by HPLC. The yield of NC-TPP mirrored that of TPP during systematic variation of reaction parameters but was consistently lower ($\leq$7.5%). The rate of NC-TPP formation also resembled that of TPP. Excess pyrrole was not required to form NC-TPP. About 2-fold more NC-TPP was obtained with BF_3-etherate compared with TFA catalysis. TPS was observed in only a few of the reactions examined. The yield of TPS peaked early and declined well before the maximum yields of TPP and NC-TPP were reached. The highest yield of TPS observed was 1.2%. TPS was produced in higher yields by TFA compared with BF_3-etherate catalysis. Additional pigments with chromatographic properties spanning the range of TPP and NC-TPP were observed in very low yield but were not characterized. N-confused tetramesitylporphyrin was isolated from the reaction of mesitaldehyde and pyrrole under BF_3-ethanol cocatalysis. Examination of the Adler reaction of benzaldehyde and pyrrole revealed the presence of NC-TPP and TPS in the filtrate but not in the crystalline TPP material. The substantial chromatographic differences between the porphyrins and N-confused porphyrins make for straightforward isolation of the purified porphyrin devoid of contaminating N-confused porphyrin. These studies indicate that the scope of conditions yielding NC-TPP is extremely broad.

Introduction

In 1994, the groups of Latos-Grazynski[1] and Furuta[2] independently described the isolation of a porphyrin isomer in about 5% yield from the acid-catalyzed condensation of pyrrole and an aryl aldehyde followed by oxidation. The isomer, a 2-aza-21-carba-5,10,15,20-tetraarylporphyrin (also called carbaporphyrin or N-confused or N-inverted porphyrin), possesses seven α-linkages and one β-pyrrole linkage rather than all α-linkages as in the parent porphyrin. In both cases, the condensation conditions were somewhat unusual. Latos-Grazynski et al. used 70 mM pyrrole and 40 mM *p*-tolualdehyde in CH_2Cl_2 at room temperature with 8 mM BF_3-etherate catalysis,[1] whereas Furuta et al. used equimolar pyrrole and benzaldehyde in the solvent *tert*-butyl alcohol/CH_2Cl_2 (1:1) at room temperature with HBr catalysis.[2] In 1995, Latos-Grazynski's group used 24 mM pyrrole and 8 mM benzaldehyde with 3 mM BF_3-etherate catalysis and isolated tetraphenylsapphyrin in 1.1% yield.[3] The reaction of benzaldehyde and pyrrole yielding tetraphenylporphyrin (TPP), N-confused TPP (NC-TPP), and tetraphenylsapphyrin (TPS) is shown in Scheme 1. No reports have appeared in which the yields of all three macrocycles (TPP, NC-TPP, and TPS) have been quantitated under conditions using excess pyrrole[1,3] or HBr catalysis in protic solvents[2] or under the more typical conditions of equimolar pyrrole and benzaldehyde in either refluxing propionic acid[4] or CH_2Cl_2 at room temperature with TFA or BF_3-etherate catalysis.[5]

The isolation of NC-TPP and TPS from the reaction of benzaldehyde and pyrrole raised a number of important questions beyond general interest in the new macrocycles.[6−8] (1) How widespread are NC-TPP and TPS in one-flask porphyrin syntheses? (2) Are ostensibly pure porphyrin preparations contaminated with N-confused porphyrin and sapphyrin? (3) Are other porphyrinic macrocycles readily isolable? (4) How does the presence of NC-TPP and TPS affect our understanding of the reaction mechanism?

In this paper, we describe our studies aimed at addressing these questions. We have investigated the effects of numerous reaction parameters on the yields of TPP, NC-TPP, and TPS obtained in the one-flask room-temperature porphyrin synthesis. The parameters studied include TFA and BF_3-etherate catalysis, acid concentration, reactant (pyrrole and benzaldehyde) concentrations,

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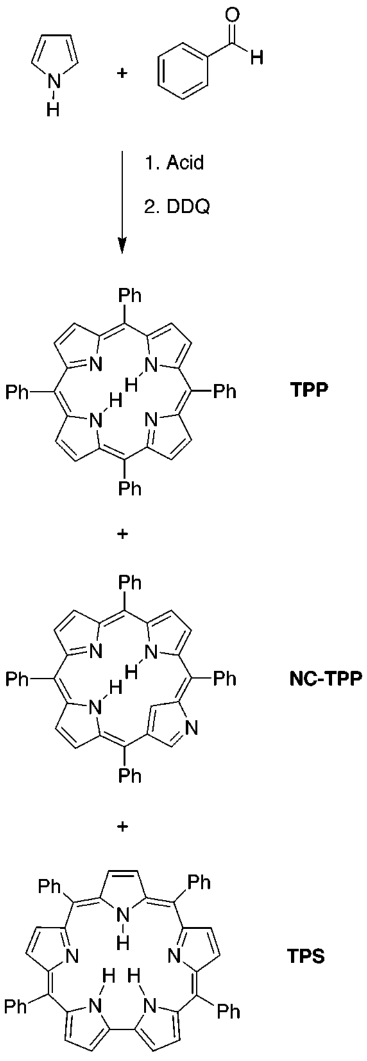
Scheme 1



reactant ratios, the addition of salt, and reaction times. These studies revealed that NC-TPP is formed under essentially all conditions leading to TPP, whereas TPS was found to a more limited extent. Accordingly, we have delineated the chromatographic properties of NC-TPP to avoid contamination of TPP with NC-TPP. To extend our studies concerning the formation and isolation of N-confused porphyrins, we have also identified and isolated N-confused tetramesitylporphyrin (NC-TMP) formed from the BF_3-ethanol cocatalyzed reaction of mesitaldehyde and pyrrole (1:1) leading to tetramesitylporphyrin (TMP). Additionally, the Adler synthesis[4] of TPP in refluxing propionic acid was examined for NC-TPP and TPS formation. Taken together, these studies establish the scope of the formation of NC-TPP and TPS under diverse reaction conditions.

Experimental Section

Materials. Pyrrole (Acros) was distilled from calcium hydride, stored at −15 °C, and used prior to any discoloration. CH_2Cl_2 (Fisher, ACS grade) used as reaction solvent was distilled from potassium carbonate and stored over 4 Å Linde molecular sieves. Benzaldehyde (Aldrich, 99.5%), mesitaldehyde (Acros, 98%), TFA (Aldrich), BF_3-etherate (Aldrich, redistilled grade), and DDQ (Aldrich) were used as received. Analytical glass-backed silica gel 60 plates (EM Science) and alumina oxide 60 plates (E. Merck) were used for TLC. Column chromatography was done using silica gel (Baker, 40 μm) or Brockman basic alumina (Fisher, 60−325 mesh, activity I) deactivated to activity II. Activity II alumina was obtained by adding 3 mL H_2O to 100 g alumina with intermittent shaking. All other materials and solvents were used as received.

Isolation of TPP, NC-TPP, and TPS for HPLC Calibration. The one-flask method of Latos-Grazynski reported for the synthesis of TPS[3] was used with slight modifications. Samples of benzaldehyde (6.1 mmol) and pyrrole (18.2 mmol) were added to CH_2Cl_2 (750 mL), then BF_3-etherate was added (2.3 mmol), and the solution was stirred for 1 h at room temperature. *p*-Chloranil (6.1 mmol) was then added, and the mixture was refluxed for 1 h. The mixture was concentrated and then purified by column chromatography. Column chromatography on basic alumina (activity grade II) with CH_2Cl_2 gave a mixture of TPP, TPS, NC-TPP, and a variety of other pigments. (Note that higher activity basic alumina produced strong retention of TPS and NC-TPP, whereas lower activity basic alumina resulted in poor retention of undesired, more polar materials.) A second basic alumina column chromatography was performed with hexanes and CH_2Cl_2 (beginning with 25% CH_2Cl_2 and ending with 100% CH_2Cl_2, increasing at about 25% intervals). TPP eluted first with 25% CH_2Cl_2, TPS eluted with about 50% CH_2Cl_2, and NC-TPP eluted with about 75% CH_2Cl_2. TPP and NC-TPP eluted as dark bands, whereas TPS did not produce an obvious band. A variety of other pigments also eluted between TPP and NC-TPP. Fractions containing TPP and NC-TPP were identified by UV−vis spectroscopy and comparison to published spectra.[2] Detection of TPS-containing fractions by UV−vis spectroscopy was difficult as a result of the low TPS concentration; small shoulders at 491 and 517 nm on the main absorption band (centered at 420 nm) were the only indication.[3] TPP was further purified by silica gel chromatography with CH_2Cl_2, and NC-TPP was further purified by silica gel chromatography with CH_2Cl_2 containing 1% triethylamine (TEA). TPP and NC-TPP were each recrystallized from methanol and CH_2Cl_2. The recrystallization of NC-TPP resulted in poor recovery. TPS was further purified by silica gel chromatography with CH_2Cl_2 containing TEA. This purification required close attention to the concentration of TEA, with 0.5−2% being typical. The chromatography was monitored by UV−vis spectroscopy. TPS was not recrystallized owing to the small amount of isolated material. TPP was isolated in 10% yield (90 mg), NC-TPP in 3% yield (30 mg), and TPS was isolated in about 0.5% yield (4 mg). The yield of TPS was slightly lower than the literature report of 1.1%.[3] Analytical data for NC-TPP and TPS (UV−vis, ^1H and ^{13}C NMR, and LD-MS) were identical to published data.[1−3] The NC-TPP was identical to an authentic sample provided to us by Latos-Grazynski's group.

General Reaction Conditions. CH_2Cl_2, pyrrole, and benzaldehyde were dispensed into 20-mL vials containing a micro stir bar. The volume of CH_2Cl_2 was selected so that the final volume of the reaction mixture would be 10 mL, assuming additivity of volumes. Benzaldehyde and pyrrole were dispensed as neat reagent or as 1 or 0.1 M stock solutions in CH_2Cl_2, depending on the desired final concentration. For experiments using salt, finely ground, dried NaCl was added. The reactions were initiated by addition of TFA or BF_3-etherate (neat acid or 1 or 0.1 M stock solutions in CH_2Cl_2). The reaction mixtures were stirred, tightly capped, and shielded from light for the desired length of time. The reactions were terminated by addition of DDQ. For 10 mM reactions, DDQ (35 mg, 0.15 mmol) was used. For reactions at higher concentration, 0.85 equiv of DDQ (based on limiting pyrrole or benzaldehyde; 200 mg for 100 mM reactions) was used. The workup for analysis began 1 min after DDQ addition. One-hour reactions were done in parallel at 12 min intervals.

Preanalysis Reaction Workup. One minute after DDQ oxidation, the samples were basified by addition of triethylamine (8-fold molar excess relative to acid). Addition of triethylamine was crucial for accurate detection of NC-TPP, otherwise NC-TPP was removed during the pre-HPLC sample cleanup (see Supporting Information). Strongly adsorbing black materials were removed prior to HPLC sample analysis

Table 1. Comparison of Yields Obtained under Selected Reaction Conditions[a]

entry[a]	acid	[PhCHO], mM	[pyrrole], mM	NaCl, equiv[b]	%TPP (SD)[c]	%NC-TPP (SD)[c]	% TPS
1	BF_3-etherate, 8 mM	40	70		17[d] (3.7)	6.1[d](1.3)	0
2	BF_3-etherate, 3 mM	8	24		9.2 (2.0)	2.9 (0.7)	0.6[e]
3	BF_3-etherate, 1 mM	10	10		27 (4.3)	5.1 (0.7)	0
4	BF_3-etherate, 1 mM	10	10	25	49 (5.1)	5.4 (0.6)	0
5	BF_3-etherate, 10 mM	100	100		24 (1.2)	5.6 (0.3)	0
6	BF_3-etherate, 10 mM	100	100	1	42 (2.5)	5.8 (1.0)	0
7	TFA, 20 mM	10	10		39 (1.8)	2.2 (0.2)	<0.2
8	TFA, 20 mM	10	10	25	39 (1.7)	2.0 (0.2)	0
9	TFA, 64 mM	100	100		28 (1.4)	4.0 (0.3)	<0.2
10	TFA, 64 mM	100	100	1	28 (1.0)	3.9 (0.2)	0

[a] All reactions were performed in CH_2Cl_2 at room temperature for 1 h, followed by DDQ oxidation. The yields were determined by HPLC. For reaction conditions employed in entries 3–10, see refs 5, 12, and 13. [b] Equivalents relative to pyrrole. [c] The standard deviation from the mean (generally 7–8 experiments). [d] The reaction of *p*-tolualdehyde and pyrrole afforded the porphyrin in 16% yield and the N-confused porphyrin in 4% yield (ref 1). [e] TPS has been isolated in 1.1% yield (ref 3).

by passing a carefully measured volume of crude reaction mixture (1.5 mL for 10 mM reactions or 0.5 mL for reactions at higher concentration) through a Pasteur pipet column packed with 1.4 g of activity II basic alumina. The sample was eluted with three 1-mL portions of CH_2Cl_2. Solvent was driven off the column by application of mild pressure using a handheld pipet tool. The eluant was transferred immediately to an autosampler vial and capped. Sample workup was performed in duplicate for each reaction. Agreement between the duplicate samples was consistently good.

Analysis. HPLC analysis was performed using a Hewlett-Packard 1100 series HPLC with a quaternary pump, an autosampler, thermostated column compartment at 25 °C, and a diode array UV–vis detector. A silica gel analytical column was used (Alltech, Altima, 4.6 mm × 250 mm) with an isocratic solvent mixture of 92.5% hexanes and 7.5% acetone. The hexanes solvent was 50% water saturated by mixing equal volumes of dry hexanes and hexanes stored over water.[9] The solvent flow rate was controlled as follows: $T = 0-5$ min, 1 mL/min; $T = 5-7$ min, linear increase–2.5 mL/min; T = 7–10.5 min, 2.5 mL/min; $T = 10.5-11.5$ min, linear decrease to 1 mL/min; and $T = 11.5-13$ min, 1 mL/min. The solvent front occurred at 2.5 min, TPP eluted at 5.0 min, TPS eluted at 7.9 min, and NC-TPP eluted at 9.9 min. Detection was performed at the following wavelengths: TPP, 417 and 590 nm; TPS, 490 nm; and NC-TPP, 438 nm. Further HPLC method development information and representative chromatograms are provided in the Supporting Information. The detection limits for TPP, TPS, and NC-TPP were 3, 6, and 3 pmol, respectively. (For 10 mM reactions, these detection limits correspond to the following yields: TPP = 0.2%, TPS = 0.4%, and NC-TPP = 0.2%. For 100 mM reactions, these detection limits correspond to the following yields: TPP = 0.2%, TPS = 0.3%, and NC-TPP = 0.2%.) To provide a comparison for the HPLC yield of TPP, samples were examined by UV–vis absorption spectroscopy as described previously.[5]

Analysis Calibrations. The HPLC was calibrated using stock solutions of TPP, NC-TPP, and TPS. Retention times and peak areas were very stable over multiple analyses. The calibration was repeated periodically, and no significant change was observed. For accurate TPP quantification, injection volumes needed to be 3 μL or less in order to avoid splitting of the TPP peak due to the injection solvent. Reaction workup calibration (correction for workup dilution) was done by comparing HPLC analyses of a mixture of TPP and NC-TPP for which a portion of the mixture was directly analyzed and a second portion was subjected to the workup conditions (vide supra). This calibration was performed multiple times with excellent repeatability (2% variance). The ratio of TPP and NC-TPP was not altered in the workup.

TMP and NC-TMP. Pyrrole and mesitaldehyde were reacted following a refined method for the preparation of TMP.[10] A solution of pyrrole (7.3 mmol) and mesitaldehyde (7.3 mmol) in 98 mL of $CHCl_3$ (ethanol-free, stabilized with amylenes) was treated with ethanol (10 mmol) and BF_3-etherate (1.8 mmol) at room temperature. The solution was stirred for 3 h, and then DDQ (5.7 mmol) was added followed a few minutes later by triethylamine (14.3 mmol). The reaction mixture was concentrated and purified by column chromatography (identically as described for the isolation of TPP and NC-TPP). TMP was isolated in 25% yield (350 mg), and NC-TMP was isolated in 3% yield (45 mg). TMP was recrystallized from methanol and CH_2Cl_2. NC-TMP was recrystallized from methanol/CH_2Cl_2 and from methanol/benzene. In both cases, the recovery of NC-TMP from the recrystallization was low (50%) and did not improve the purity. The analytical data for TMP were identical to published data.[11] **NC-TMP:** UV–vis λ_{max} (CH_2Cl_2, nm, log ϵ) 435 (5.15), 532 (4.01), 571 (3.83), 721 (3.91), λ_{em} (CH_2Cl_2, $\lambda_{exc} = 532$ nm) 733, 811 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ −4.92 (s, 1 H), −2.07 (bs, 2 H), 1.91 (s, 12 H), 1.92 (s, 6 H), 1.94 (s, 6 H), 2.57 (s, 3 H), 2.59 (s, 3 H), 2.61 (s, 6 H), 7.24 (s, 4 H), 7.27 (s, 4 H), 8.33–8.41 (m, 4 H), 8.56 (d, 1 H, $J = 4.5$ Hz), 8.58 (d, 1 H, $J = 4.5$ Hz), 8.82 (s, 1 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.6, 21.8, 21.9, 29.9, 101.3, 115.1, 116.8, 122.7, 124.4, 125.3, 127.5, 128.1, 134.0, 134.3, 134.6, 136.1, 136.6, 136.9, 137.1, 137.9, 138.3, 138.8, 139.1, 139.2, 139.5, 139.6, 139.9, 150.2, 156.3, 157.4, 157.6; $C_{56}H_{54}N_4$ calcd exact mass 783.4427, obsd *m/z* 783.1 (LD-MS), obsd *m/z* 783.4437 (FAB-MS).

Results and Discussion

Distribution of TPP, TPS, and NC-TPP Yields. The yields of TPP, TPS, and NC-TPP were examined as a function of six reaction parameters: (1) TFA and BF_3-etherate, (2) acid concentration, (3) pyrrole and benzaldehyde (reactants) concentration, (4) pyrrole:benzaldehyde ratio, (5) salt, and (6) time. These parameters are the most frequently examined variables in the optimization of one-flask room-temperature porphyrin syntheses. All reactions were performed in CH_2Cl_2 at room temperature at 10-mL scale, and yields were determined by HPLC. Selected results are presented here with results for all experiments provided in the Supporting Information.

The reaction of benzaldehyde and pyrrole was performed under representative conditions reported in the literature, and the yields of TPP, NC-TPP, and TPS were determined (Table 1). The method of Latos-Grazynski, using excess pyrrole, produced TPP, NC-TPP, and TPS as expected (entries 1 and 2). The use of equimolar pyrrole and benzaldehyde also produced appreciable

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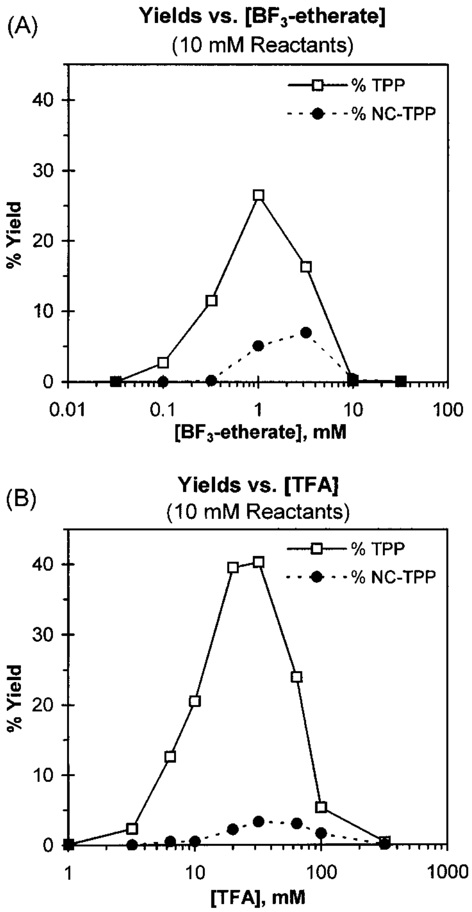

Figure 1. Yields of TPP and NC-TPP as a function of acid concentration. All reactions were performed for 1 h.

amounts of NC-TPP (up to 5.8%) but little or no TPS (entries 3−10). The ratio of TPP:NC-TPP ranged from 3:1 to 20:1. Larger amounts of NC-TPP were generally observed with BF_3-etherate than with TFA catalysis. NC-TPP is clearly a byproduct of the acid-catalyzed condensation of pyrrole and benzaldehyde under the usual porphyrin-forming conditions, not just under the conditions of excess pyrrole reported in the literature.[1,3]

The concentration of acid catalyst has a significant effect on the rate and course of reaction.[5,12] Thus, the yields of TPP, NC-TPP, and TPS were measured as a function of TFA or BF_3-etherate concentration with 10 mM reactants. The yield of NC-TPP generally tracked that of TPP (Figure 1). For the optimal concentrations of acid, higher yields of NC-TPP were obtained with BF_3-etherate than with TFA. The TPS yield was less than 1% under all conditions examined (not shown). An identical study at 100 mM reactants gave similar results (see Supporting Information).

The yield of TPP depends on the concentration of benzaldehyde and pyrrole, with maximal yields generally observed at 10 mM.[5,12] Accordingly, the yields of TPP, NC-TPP, and TPS were measured as a function of benzaldehyde and pyrrole concentrations with fixed concentrations of TFA (20 mM) or BF_3-etherate (1 mM). Again, the yield of NC-TPP generally tracked that of TPP but at a diminished level (Figure 2). The TPS yield was less than 1% under all conditions examined (not shown).

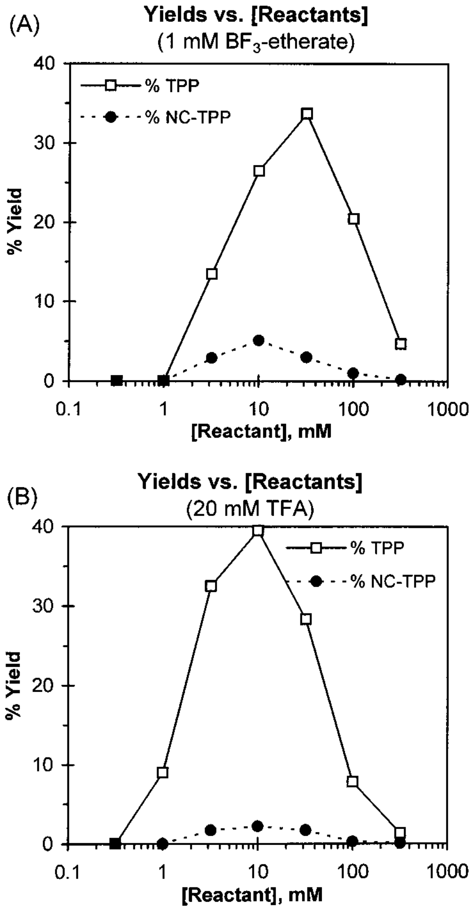

Figure 2. Yields of TPP and NC-TPP as a function of reactant concentration. All reactions were performed for 1 h.

An identical study with higher acid concentrations gave similar results (see Supporting Information).

The reports by Latos-Grazynski of the formation of N-confused tetra-*p*-tolylporphyrin[1] and TPS[3] with the use of excess pyrrole prompted us to examine the yields of TPP, NC-TPP, and TPS as a function of the pyrrole: benzaldehyde ratio. For pyrrole at 100 mM, benzaldehyde was varied from 12.5 to 800 mM with BF_3-etherate or TFA catalysis. The same experiments were performed with benzaldehyde at 100 mM, and pyrrole varied from 12.5 to 800 mM. The results are displayed in Figure 3. In all cases examined, the yield of TPP was peaked at equimolar pyrrole and benzaldehyde. In general, the distribution of NC-TPP was slightly skewed toward excess pyrrole, but the peak remained at or near equimolar pyrrole and benzaldehyde. This result shows that excess pyrrole is not required for the formation of NC-TPP. The TPS yield was less than 1% under all conditions examined (not shown). A study with one reactant fixed at 10 mM and the other reactant spanning the range of 1.25−80 mM gave similar results (see Supporting Information).

Recently, the beneficial effects of added salt on the yield of porphyrin were reported.[13] The salt effect can nearly double the yield of TPP with BF_3-etherate as the catalyst. The effect of salt on the yields of NC-TPP and TPS was examined by performing reactions at 10 and 100 mM in the presence of NaCl (Figure 4). Although

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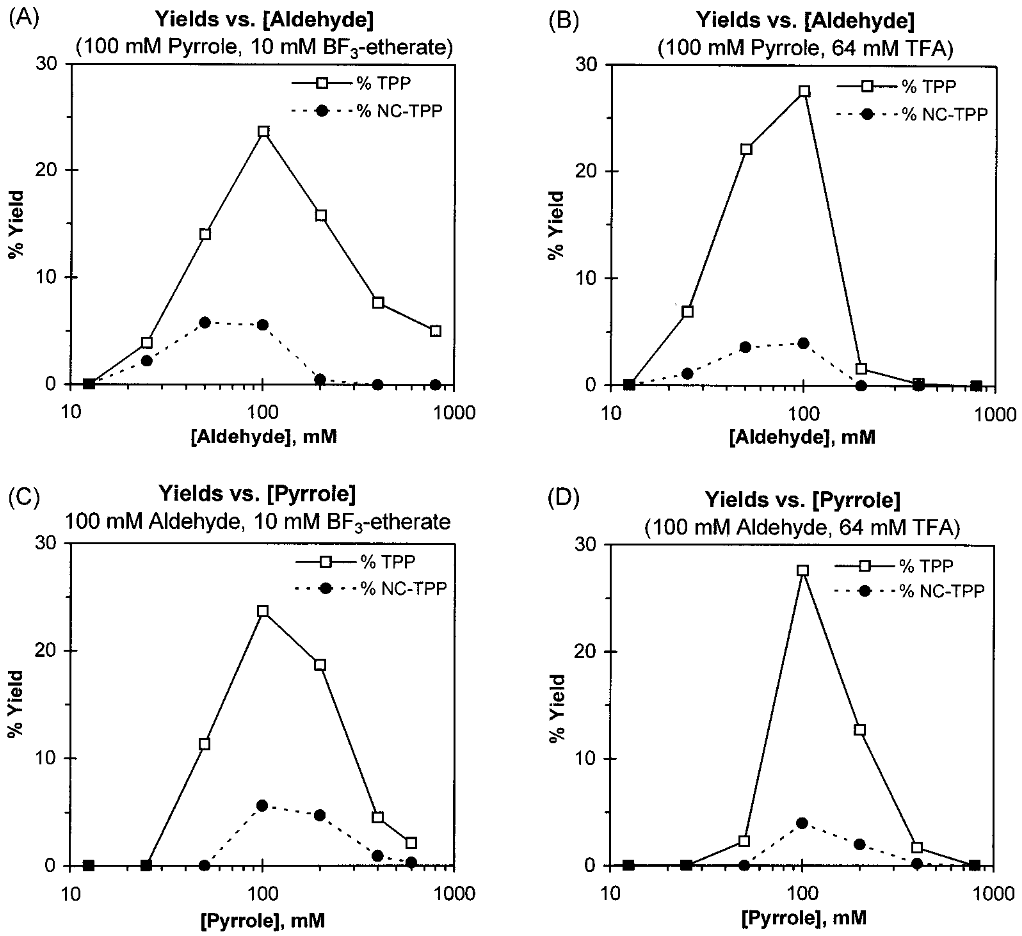

Figure 3. Yields of TPP and NC-TPP as a function of benzaldehyde:pyrrole ratio. All reactions were performed for 1 h.

the expected increase in TPP yield was observed in the BF_3-etherate catalyzed reactions, very little enhancement of the NC-TPP yield occurred. With TFA catalysis, no salt effect was observed for either the TPP or NC-TPP products. The yield of TPS was <1% regardless of the presence of salt with either catalyst (data not shown).

The yields of TPP, NC-TPP, and TPS were monitored over time for eight variations of the one-flask room-temperature porphyrin synthesis (10 and 100 mM reactants for BF_3-etherate, TFA catalysis, salt or no salt).[5,12,13] Time points were obtained from 15 s to 30 h. Figure 5 summarizes the results of the BF_3-etherate experiments. In all cases, the yield of NC-TPP over time mirrored that of TPP. Both species reached a maximum at a similar point and showed similar decreases in yield at longer time points. Adding NaCl increased the rate of formation for both species, but their kinetic profiles remained similar. Very little TPS (<0.2%) was detected at any time under BF_3-etherate catalysis. The results from the TFA experiments (see Supporting Information) are very similar with only two exceptions: (1) No salt effect was observed. (2) TPS was readily detected at early times but not after 1 h. At 10 mM reactants, the yield of TPS peaked at 0.5% between 8 and 15 min and was no longer detected by 30 min. At 100 mM reactants, the yield of TPS peaked at 1.1% between 30 s and 1 min and was no longer detected by 15 min. This observation of rapid TPS formation and decline explains the general absence of TPS in the majority of experiments using a 1-h reaction time.

The extensive experimentation concerning the formation of NC-TPP allowed identification of conditions leading to 5.5–7.5% NC-TPP. The conditions giving the highest yields are listed in Table 2. A wide variety of catalyst concentrations and reactant concentrations can be employed, but the pyrrole:benzaldehyde ratio is constrained to the range of 0.5–2. For the synthesis of TPS, the best conditions found were 100 mM reactants with 64 mM TFA in CH_2Cl_2 at room temperature for 30 s prior to oxidation, which gave TPS in 1.2% yield.

Chromatographic Properties of NC-TPP and TPS. Chromatography of NC-TPP and TPS was initially performed to provide materials for HPLC method development and calibration. The chromatographic properties of NC-TPP acquired more significance when NC-TPP was observed under a wide range of reaction conditions in yields up to 7.5%, as reported in the previous section. Our initial attempts to isolate NC-TPP and TPS, using the published procedures of both Latos-Grazynski[1,3] and Furuta[2] were unsuccessful, with only TPP being isolated. The activity I grade basic alumina and silica gel used initially were found to strongly adsorb NC-TPP and TPS. In fact, the chromatographic behavior of NC-TPP and TPS more closely resembles the black byproducts of the reaction than TPP. This conclusion is supported by a comparison of TLC retention characteristics of the three macrocycles on silica and alumina with a variety of developing solvents (Table 3). On silica, NC-TPP and TPS do not elute at all with the usual development solvents for TPP. On alumina, NC-TPP and TPS elute with

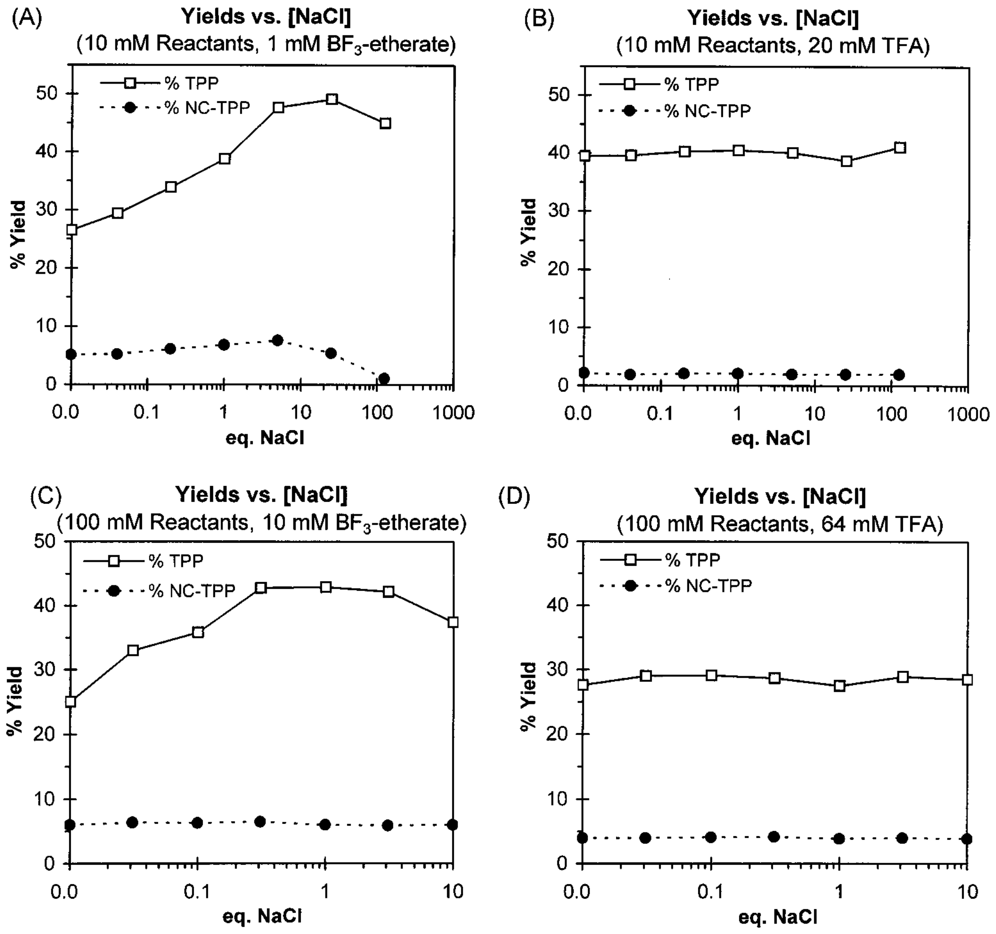

Figure 4. Yields of TPP and NC-TPP as a function of amount of NaCl. All reactions were performed for 1 h.

slightly higher R_f than the black byproducts and with lower R_f than TPP when developing with CH_2Cl_2 and less polar solvents. Chromatography, as described in the Experimental Section, allowed isolation of NC-TPP and TPS in about 95% purity with little difficulty. Given the substantial polarity differences of TPP and NC-TPP, TPP purified by chromatography is likely not contaminated with NC-TPP. The removal of NC-TPP is especially likely for samples that have not been neutralized prior to chromatography because the NC-TPP is known to be more basic than TPP.[1]

Observation of Additional Pigments. A key question concerns whether other porphyrinic macrocycles are present in significant abundance in the crude reaction mixture. Such macrocycles could include corrole,[14] rubyrin, pentaphyrin, hexaphyrin, and larger expanded porphyrins, multiply N-confused porphyrins, as well as yet uncharacterized structures. In our attempts to isolate NC-TPP (and NC-TMP, vide infra), about 4−6 additional pigments (distinct from the nondescript black background materials) were detected which eluted later than the porphyrin and earlier than the N-confused porphyrin.[15] The yield of those pigments, as estimated by gravimetric analysis, was uniformly low (less than that of TPS). Likewise, in the HPLC analysis of the reaction mixtures, a handful of peaks in addition to TPP, TPS, and NC-TPP were detected. No single peak appeared consistently under a wide range of conditions, and very few of the peaks were of significant area, indicating low yield if the molar extinction coefficient is similar to TPP, NC-TPP, or TPS. Although the nature of these pigments is unknown, none is apparently produced in significant yield. The yield of cyclic products (of polarity bracketed by TPP and NC-TPP) can be summarized as follows: TPP $>$ NC-TPP $\gg$ TPS $\approx$ other pigments. Thus, within the range of conditions examined, the one-flask synthetic methodology involving equimolar reactants[5] appears best suited for the preparation of porphyrin and N-confused porphyrin.

Survey of NC-TPP and TPS in the Adler Reaction. We examined the reaction of benzaldehyde and pyrrole (0.27 M each) in refluxing propionic acid exposed to air (Adler reaction)[4] to determine if NC-TPP forms under these conditions and if NC-TPP contaminates the isolated crystals of TPP. The formation of TPS in the Adler reaction has been reported.[3] The TPP crystals and filtrate were examined by HPLC. The crystalline material was free of NC-TPP and TPS. The filtrate contained NC-TPP in about 1% overall yield and TPS in about 0.5% yield. Thus, it appears that crystallization effectively removes NC-TPP and TPS from the TPP.

N-Confused Tetramesitylporphyrin. The reaction of pyrrole and mesitaldehyde with BF_3-ethanol cocataly-

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[14] A report has appeared concerning the formation of tris(2,6-dinitro-4-*tert*-butylphenyl)corrole, but yield and complete analytical data have not been published. See: Rose, E.; Kossanyi, A.; Quelquejeu, M.; Soleilhavoup, M.; Duwavarn, F.; Bernard, N.; Lecas, A. *J. Am. Chem. Soc.* **1996**, *118*, 1567−1568.

[15] After elution of NC-TPP, additional dark material remained on the column (largely, but not entirely, quinone and hydroquinone materials). No attempt was made to further fractionate that material to look for additional polar macrocyclic pigments.

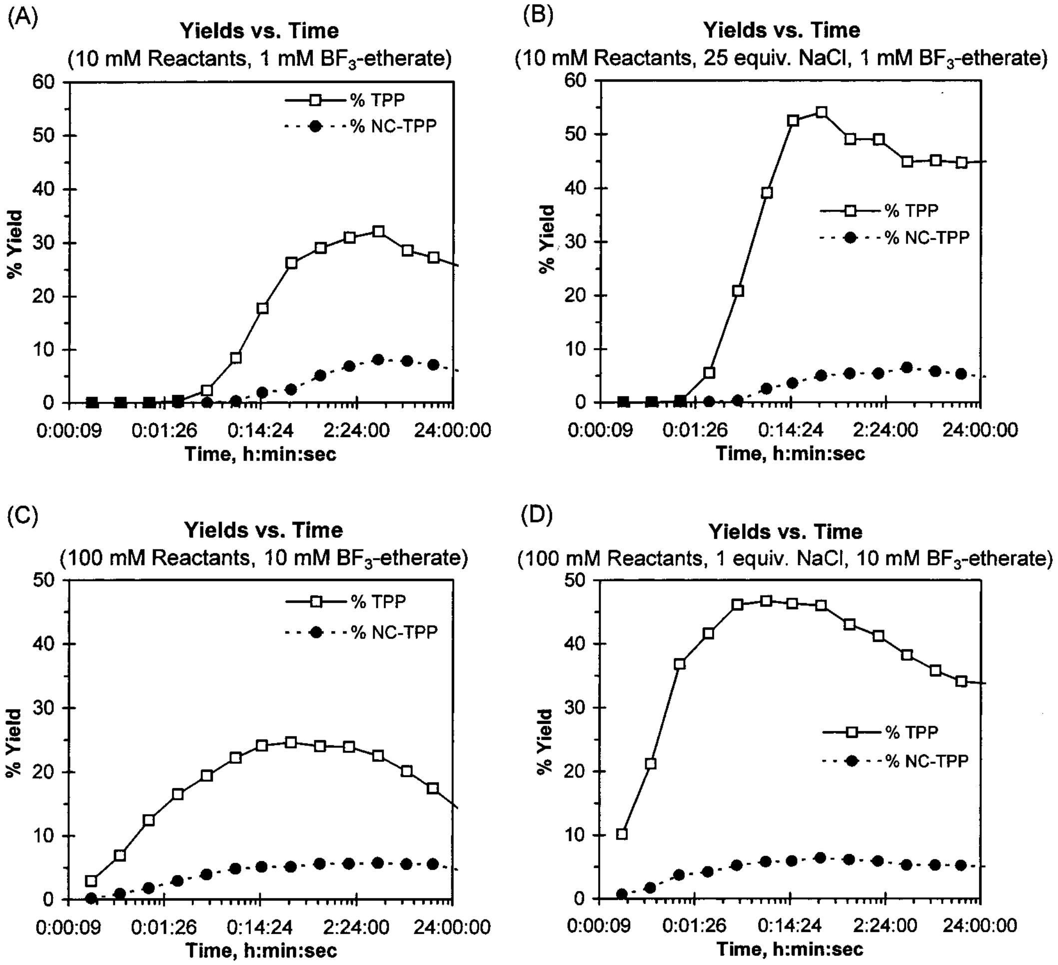


Figure 5. Kinetic profiles of TPP and NC-TPP yields for BF$_3$-etherate catalyzed reactions. Note the log scale used for displaying the time axis.

Table 2. Summary of Conditions Producing Highest Yields of NC-TPP[a]

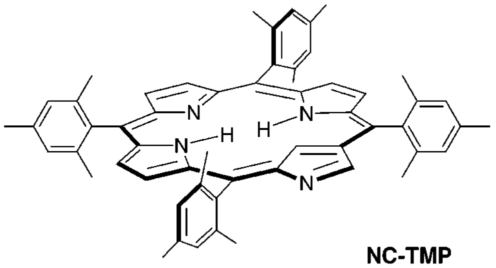
entry	BF$_3$-etherate, mM	[PhCHO], mM	[pyrrole], mM	[NaCl], equiv[b]	%NC-TPP	%TPP
1	3.2	32	32		7.5	32
2	3.2	10	10		7.0	16
3	3.2	32	32	3.2	7.0	41
4	1	10	5		6.3	30
5	10	50	100	1	6.3	20
6	8	40	70		6.1	17
7	1	3.2	3.2	78	6.0	41
8	10	100	100	1	5.8	42
9	10	50	100		5.8	14
10	10	100	100		5.6	24

[a] All reactions were performed in CH$_2$Cl$_2$ at room temperature for 1 h, followed by DDQ oxidation. The yields were determined by HPLC. [b] Equivalents relative to pyrrole.

sis smoothly affords TMP.[11] These condensation conditions provide the basis for the synthesis of a wide variety of facially encumbered porphyrins.[16] The reaction of pyrrole and mesitaldehyde by means of a refined method[10] was examined for the presence of the N-confused tetramesitylporphyrin (NC-TMP). Column chromatography of the crude reaction mixture afforded TMP (25%) and NC-TMP (3%). NC-TMP was isolated in about 95% purity using chromatographic conditions identical to those for NC-TPP, indicating that the facial encumbrance of the mesityl groups did not significantly alter the chromatographic behavior. These results provide further evidence for the generality of formation of N-confused porphyrins during pyrrole–aldehyde condensations, as well as the facile removal of the N-confused porphyrin via chromatography.

Table 3. Comparison of TLC R_f Values for TPP, NC-TPP, and TPS

	silica			alumina		
solvent	TPP	NC-TPP	TPS	TPP	NC-TPP	TPS
toluene	0.80	0.0	0.0	0.82	0.09	0.27
1:1 hexanes/CH$_2$Cl$_2$	0.51	0.0	0.0	0.77	0.17	0.30
CH$_2$Cl$_2$	0.88	0.0	0.00	0.92	0.65	0.83
CH$_2$Cl$_2$, 1% TEA	0.90	0.05	0.05	0.94	0.74	0.91
CH$_2$Cl$_2$, 5% MeOH	0.98	0.33	0.40	0.97	0.97	0.97
THF	0.84	0.84	0.84	0.88	0.85	0.87
acetone	0.88	0.85	0.86	0.89	0.89	0.89



NC-TMP

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(16) Lindsey, J. S. In *Metalloporphyrin-Catalyzed Oxidations*; Montanari, F., Casella, L., Eds.; Kluwer Academic Publishers: The Netherlands, 1994; pp 49–86.

Mechanistic Implications. The generality of the production of NC-TPP under a variety of porphyrin-forming conditions shows that the formation of β-pyrrole linkages is not restricted to the unusual conditions reported earlier.[1,2,3] Rather, β-pyrrole linkages provided a route for the diversion of starting materials under most conditions that produced porphyrin in this study. The distribution of NC-TPP relative to TPP suggests that the two macrocycles share a similar reaction pathway. Detection of TPS shows that oligomers larger than tetramers are also able to cyclize. The reduced precursor of TPS is distinguished from those of TPP and NC-TPP by the fact that it rapidly forms in low yield and then rapidly decreases in yield. Differences between TFA and BF_3-etherate catalysis were also observed, with BF_3-etherate producing more NC-TPP and TFA leading to more TPS. Whether factors other than acid strength are also involved is unknown. The exact distribution of all products (porphyrin, dipyrrin shunt products,[11] β-pyrrole linked products, bipyrrole-containing products, other macrocycles, and linear oligomers), the effects of changes in reaction conditions, and the way in which the distribution changes over time remain to be determined.

Conclusions

The yields of TPP, NC-TPP, and TPS formed under a variety of conditions used in one-flask porphyrin-forming reactions have been determined. TPP was the major macrocyclic product formed under all conditions examined. NC-TPP was present under a wide range of conditions (including the Adler method), with a maximal yield of 7.5%. The distribution of NC-TPP mirrored that of TPP, and higher yields were obtained under BF_3-etherate catalysis. TPS was formed in higher yields under TFA catalysis, but all yields were quite low (generally $<1\%$). Clearly, special conditions are not required for the formation of NC-TPP. The chromatographic properties of the porphyrins and N-confused porphyrins examined are substantially different, making for straightforward isolation of the purified porphyrin devoid of contaminating N-confused porphyrin. A handful of pigments have been detected with chromatographic properties spanning the range from TPP to NC-TPP, albeit in low yield.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for NC-TMP, HPLC method development information, representative HPLC chromatograms, method verification and repeatability data, and complete summaries of results from all experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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